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[54] **METHOD OF TREATMENT FOR DECREASING MORTALITY RESULTING FROM CONGESTIVE HEART FAILURE**

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[58] Field of Search 514/411, 423, 514/223.2, 223.5, 471, 175

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,888,179	12/1989	Appelgren et al.	424/480
5,308,862	5/1994	Ohlstein	514/411
5,312,828	5/1994	Finkelstein et al.	514/381

OTHER PUBLICATIONS

J. of Cardiovascular Pharm; Senior, et al. "Effects of Carvedilol on Ventricular Arrhythmias". 1992, vol. 19, (Suppl. 1): pp. S117-S121.

J. of Cardiovascular Pharm; DasGupta, et al. "The Effects of Intravenous Carvedilol. A New Multiple Action Vasodilatory β -Blocker, in Congestive Heart Failure". 1991, vol. 18, (Suppl. 1): pp. S12-S16.

British J. of Urology; Caine, et al. "The Use of Alpha-adrenergic Blockers in Benign Prostatic Obstruction". 1976, vol. 48, pp. 255-263.

British J. of Urology; H.N. Whitfield, et al. "The Effect of Adrenergic Blocking Drugs on Outflow Resistance". 1976, vol. 47, pp. 823-827.

American J. of Cardiology; DasGupta, et al. "Value of Carvedilol in Congestive Heart Failure Secondary to Coronary Artery Disease". 1990, vol. 66, pp. 1118-1123.

Z. Kardiol; A. Buchwald, et al. "Acute Hemodynamic Effects of the Beta-blocker Carvedilol in Heart Failure". 1990, vol. 79, No. 6, pp. 424-428.

JACC; DiLenarda, et al. "Acute Hemodynamic Effects of Carvedilol Versus Metoprolol In Idiopathic Dilated Cardiomyopathy". 1991, vol. 17, No. 2, Abstract 142A.

Frontiers in CHF; D. Tepper, "Multicenter Oral Carvedilol Heart Failure Assessment". 1996, vol. 2, No. 1, pp. 39-40.

J. of Cardiovascular Pharm; DasGupta, et al. 1990, vol. 19, (Suppl. 1): pp. 562-567.

J. of Hypertension; C. Rosendorff, "Beta-blocking agents with vasodilator activity". 1993, vol. 11, (Suppl. 4): pp. S37-S40.

Cardiology; J. Lessem, et al. "Development of a Multication Beta-blocker". 1993, vol. 82, (Suppl. 3): pp. 50-58.

Drug Safety; W.J. Louis, et al. "A Risk-Benefit Assessment of Carvedilol in the Treatment of Cardiovascular Disorders". 1994, vol. 11, No. 2, pp. 86-93.

Drugs; McTavish, et al. "Carvedilol—A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy". 1993, vol. 45, No. 2, pp. 232-258.

Circulation; H. Krum, et al. "Effects of Cavedilol, a Vasodilator- β -Blocker, in Patients with Congestive Heart Failure Due to Ischemic Heart Disease". 1995, vol. 92, No. 2, pp. 212-218.

CBS-TV; CBS Evenings News, Transcript, Jan. 27, 1993, 6:30-7:00pm.

CNBC; Steals and Deals, Transcript, Jan. 29, 1993, 8:30pm.

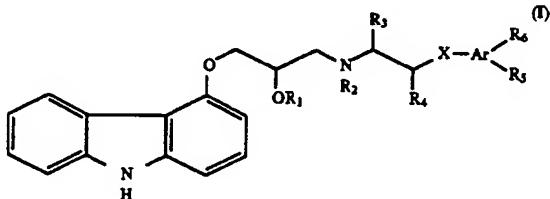
Circulation, DasGupta, et al. 1989, vol. 80, No. 4, (Suppl. II): pp. 116-117.

Drugs of Today; Ruffolo, et al. "Carvedilol (Kredex): A Novel Multiple Action Cardiovascular Agent". 1991, vol. 27, No. 7, pp. 465-492.

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[57] **ABSTRACT**

A method of treatment using a compound of Formula I:



wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-\text{CH}_2-\text{O}-$;

X is a valency bond, $-\text{CH}_2$, oxygen or sulfur;

Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-\text{CONH}_2$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkylsulphonyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy;

or a pharmaceutically acceptable salt thereof, alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of ACE inhibitors, diuretics, and digoxin for decreasing mortality resulting from congestive heart failure (CHF) in mammals, particularly humans.